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Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis

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Summary

Background The annual number of hospital admissions and in-hospital deaths due to severe acute lower respiratory infections (ALRI) in young children worldwide is unknown. We aimed to estimate the incidence of admissions and deaths for such infections in children younger than 5 years in 2010.

Methods We estimated the incidence of admissions for severe and very severe ALRI in children younger than 5 years, stratified by age and region, with data from a systematic review of studies published between Jan 1, 1990, and March 31, 2012, and from 28 unpublished population-based studies. We applied these incidence estimates to population estimates for 2010, to calculate the global and regional burden in children admitted with severe ALRI in that year. We estimated in-hospital mortality due to severe and very severe ALRI by combining incidence estimates with case fatality ratios from hospital-based studies.

Findings We identified 89 eligible studies and estimated that in 2010, 11·9 million (95% CI 10·3–13·9 million) episodes of severe and 3·0 million (2·1–4·2 million) episodes of very severe ALRI resulted in hospital admissions in young children worldwide. Incidence was higher in boys than in girls, the sex disparity being greatest in South Asian studies. On the basis of data from 37 hospital studies reporting case fatality ratios for severe ALRI, we estimated that roughly 265 000 (95% CI 160 000–450 000) in-hospital deaths took place in young children, with 99% of these deaths in developing countries. Therefore, the data suggest that although 62% of children with severe ALRI are treated in hospitals, 81% of deaths happen outside hospitals.

Interpretation Severe ALRI is a substantial burden on health services worldwide and a major cause of hospital referral and admission in young children. Improved hospital access and reduced inequities, such as those related to sex and rural status, could substantially decrease mortality related to such infection. Community-based management of severe disease could be an important complementary strategy to reduce pneumonia mortality and health inequities.

Funding WHO.

Introduction

Acute lower respiratory infections (ALRI), such as pneumonia and bronchiolitis, are a leading cause of morbidity and mortality in young children. In 2010, 1·4 million children died because of such infections,¹ resulting in a substantial burden on the health-care system. No systematically established global estimates have been made of the incidence of hospital admissions for severe ALRI in children younger than 5 years. Rudan² estimated that worldwide, 7–13% of 156 million yearly pneumonia cases might progress to severe disease and warrant admission. However, these preliminary estimates were based on findings from only 28 community-based studies of disease incidence, six of which estimated the proportion of severe episodes, and these had variable case ascertainment.

We were aware of additional high-quality data for incidence of and mortality from admissions for severe

ALRI. These data were from published and unpublished hospital-based studies with passive case ascertainment—ie, children who reported to the health facility. Therefore, we formed a Severe ALRI Working Group, a consortium of leading researchers in childhood pneumonia working mainly in developing countries, to estimate the incidence of hospital admissions and in-hospital deaths due to severe ALRI in children younger than 5 years in 2010, worldwide and for six WHO regions. Furthermore, we examined how these estimates varied by severity of episode, by sex, by distance from the hospital, and in the period 2008–10 during the influenza A H1N1 pandemic.

Methods

Search strategy and selection criteria

We undertook a systematic literature review with various search terms (appendix pp 4–6), hand searched online journals, and scanned the reference lists of identified

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See [Comment](#) page 1341

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citations. We searched Medline (Ovid), Embase, CINAHL, Global Health, Web of Science, WHOLIS, LILACS, IndMed, SIGLE for studies published between Jan 1, 1990, and March 31, 2012. We also searched three Chinese language databases: China National Knowledge Infrastructure, Wanfang Data, and Chongqing VIP for studies published in Chinese.

We included studies reporting data for hospital admission for ALRI and severe ALRI in children younger than 5 years, with data for at least 12 consecutive months, and reporting incidence or mortality for at least the first year of life. Although we assessed studies reporting incidence estimates, we included only those with well defined catchment populations or estimations of the population at risk. We excluded studies in which the case definition was not clearly defined or not consistently applied; description of the methods for estimation of the denominator population was not clear; only cause-specific ALRI incidence or mortality were reported; only incidence or mortality estimates for ALRI confirmed by chest radiograph were reported; those in which incidence or mortality were estimated with modelling techniques; or those reporting data by community-based case ascertainment. We applied no language or publication restrictions. Two investigators (HN and PH) did the search in English language databases and extracted data. Any disagreements were resolved after discussion. One investigator (JSFZ) whose first language was Chinese undertook searches and data abstraction from Chinese language databases and validated identified studies in direct discussion with HN. Unpublished studies were identified in meetings of the Severe ALRI Working Group.

The working group agreed on an approach for data analysis and interpretation and formulated common case definitions. The group either reanalysed data from their already published work with these case definitions or shared hitherto unpublished data from ongoing studies. This method resulted in analysis of substantial unpublished data, which supplemented data from review of published studies (appendix pp 14–16).

Definitions

Most investigators used modified versions of WHO case definitions for severe pneumonia (appendix pp 17–26).³ We used the terms severe and very severe ALRI because many young children present with bronchiolitis, which can be clinically indistinguishable from pneumonia. We decided that children with ALRI denoted by cough or difficulty breathing with increased respiratory rate for age, with or without indrawing of the chest wall who were admitted at the discretion of the attending physician should be referred to as having severe ALRI. We defined very severe ALRI as severe ALRI with hypoxaemia, or WHO Integrated Management of Childhood Illness danger signs, or both. Because data for hypoxaemia were limited to health facilities where pulse oximetry was available, we included studies reporting data for children

admitted with severe ALRI and any of the danger signs³ in the category of very severe ALRI (appendix pp 27–30). We recognised that children admitted with very severe ALRI would have a more life-threatening illness and regarded these patients as a subset of those with severe ALRI. We designated countries as industrialised or developing on the basis of UNICEF's classification in The State of the World's Children 2012 report. The child population estimates for 2010 are as in the UN Population Division's database, World Population Prospects: the 2010 revision.

Data imputation

For studies that did not report disease incidence for the full age range (ie, 0–59 months), we used imputation to calculate missing data by use of the median incidence rate ratio (appendix pp 7–8).^{4,5} We did a sensitivity analysis with unimputed data and noted that the final estimates did not differ significantly. If the duration of the study exceeded 12 months, but was not in exact multiples of 1 year, we calculated and reported the annualised incidence by adjusting for the population at risk.

Statistical analysis

We did a meta-analysis of data for disease incidence and case-fatality ratio and report pooled estimates and 95% CIs. We used the random effects model (DerSimonian-Laird method) because of significant heterogeneity in the data ($I^2 > 80\%$, $p < 0.0005$).⁶ Because HIV is a major risk factor for admission for severe ALRI, and the prevalence of HIV in children younger than 5 years has decreased substantially and access to highly active antiretroviral treatment has increased greatly in South Africa since 2002 (median year for the study from Soweto, South Africa),⁷ we adjusted the incidence (appendix pp 17–26) taking into consideration both determinants and used the adjusted rates when undertaking the meta-analysis (appendix pp 9–11). We used data for the period Jan 1, 1981, to Dec 31, 2010, and estimated the incidence for industrialised and developing countries and for the six WHO regions, and applied these estimates to children younger than 5 years in 2010. We used two approaches to estimate the probable number of children with episodes of severe ALRI who were not admitted and hence (by combining those estimates with our hospital estimates), the total number of severe cases in developing countries in 2010. First, we used data for health-care use (in children with reported signs of pneumonia) from Demographic Health Survey (DHS) and Multi Indicator Cluster Survey (MICS) databases from 81 surveys from developing countries as a proxy for the proportion of children with severe ALRI who sought hospital care.

For the second approach we used data from four hospital studies that recorded all admissions for severe ALRI within the setting of community-based active surveillance of all episodes of ALRI and severe ALRI

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(on the basis of WHO Integrated Management of Childhood Illness case definitions).³ This approach enabled us to estimate the proportion of children who were actually admitted (appendix p 12). We assessed variation in incidence by case definitions for disease severity and by distance from the hospital. We used incidence ratios to compare the difference in incidence between boys and girls.

To estimate in-hospital deaths due to severe and very severe ALRI, we applied the meta-estimates of the in-hospital case-fatality ratios to incidence data for admissions for severe and very severe ALRI for developing and industrialised regions. We did a sensitivity analysis to assess whether the case fatality ratio was a function of the disease incidence and noted no such relation across the developing world (appendix pp 44–45). This finding supports our decision to use a standard ratio (obtained

from the random effects model) for all developing countries. We did all data analysis with Stata (version 11.2).

Role of the funding source

The funding sources supported a meeting of the Severe ALRI Working Group in Edinburgh, UK (Aug 30–31, 2010). The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. HN had full access to all the data in the study and HN and HC had final responsibility for the decision to submit for publication.

Results

We identified 89 hospital-based studies with suitable data for incidence (figure 1); 61 were published^{7–65} (of which 14 were in Chinese and two^{9,17} had data for two different populations) and 28 were unpublished (figure 2; appendix pp 17–26). 30 studies were in rural populations, 17 in urban populations, and 42 were in a mixture of both. 25 (40%) of 62 studies from developing countries were either cohort studies or were in a demographic surveillance site; seven (11%) had a well-defined catchment area for which we estimated the population with a health-care utilisation survey, and 30 (49%) were undertaken in hospitals with well defined catchment areas. Only 43 studies (24 published and 19 unpublished; appendix pp 7–8) reported disease incidence by age group for the full age range and we imputed data for the remaining 46 studies. 19 studies (15 unpublished) reported incidence specifically for neonates (infants aged 0–27 days; appendix pp 31–32). The 62 studies from developing countries reported incidence of hospital admissions for severe ALRI in children aged 0–59 months (about 20 episodes per 1000 children per year; table 1).

Disease incidence was highest in neonates aged 0–27 days (68.6 episodes per 1000 per year, 95% CI 47.8–98.4; appendix pp 31–32) and infants aged 0–11 months (51.8 episodes per 1000 per year, 44.8–59.8). With data from 27 studies in industrialised countries, estimates of the incidence of admissions for severe ALRI was about 20 episodes per 1000 children per year in children aged 0–11 months, and about 10 episodes per 1000 children per year in those aged 0–59 months, which translate to about 12 million episodes worldwide in children younger than 5 years in 2010, with disease in neonates contributing to about 6% of this overall burden (table 1). Data from 15 unpublished studies that recorded this information showed that only about 60% of children admitted with ALRI have indrawing of the lower-chest wall (appendix pp 38–39). 36 studies (34 from developing countries) reported the incidence of admissions for very severe ALRI in children aged 0–59 months (appendix pp 27–30). We estimated that the incidence of admissions for very severe ALRI in this age group in developing countries was about five episodes per 1000 children per year, which translates to about 3 million cases worldwide

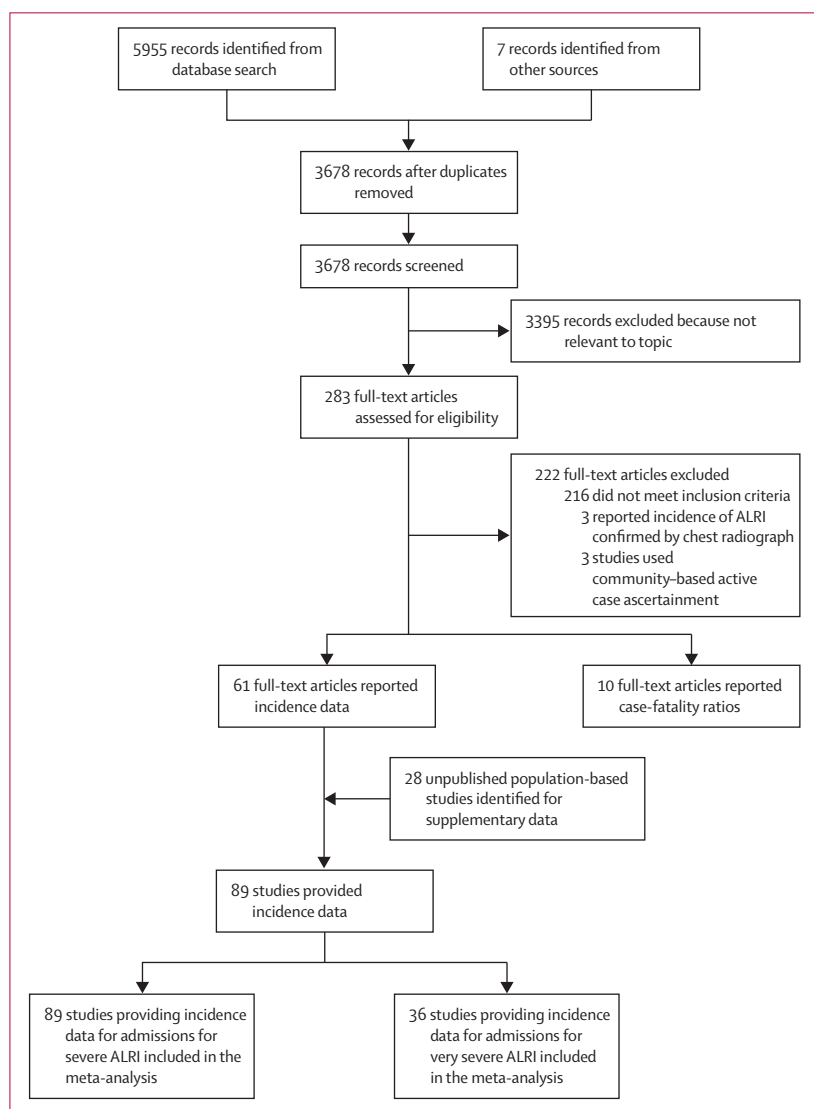
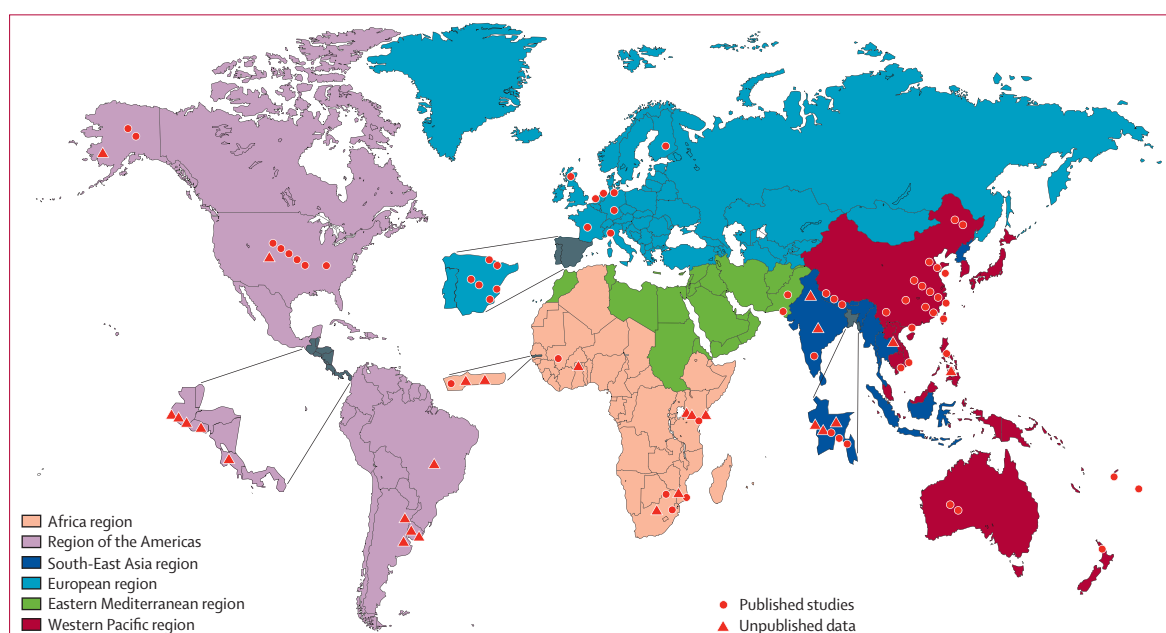


Figure 1: Flow diagram for selection of studies



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See Online for appendix

For the **China National
Knowledge Infrastructure** see
<http://www.global.cnki.net>

For **Wanfang Data** see <http://www.wanfangdata.com.cn>

For **Chongqing VIP** see <http://www.cqvip.com>

Figure 2: Location of the 89 studies by WHO region

	Africa	Americas	Eastern Mediterranean	Europe	South-East Asia	Western Pacific	Developing countries*	Industrial- ised countries	Global
Severe ALRI									
Aged <1 year									
Studies	14 (2)	20 (1)	2 (0)	14 (9)	14 (6)	25 (15)	65 (21)	24 (12)	89 (33)
Incidence†	50.8 (33.6–76.9)	46 (35.5–59.7)	27.9 (14–55.5)	14.2 (8.1–25)	48.1 (34.8–66.6)	43 (32.3–57.3)	51.8 (44.8–59.8)	19.6 (16.1–23.9)	..
Number of episodes (thousands)‡	1431 (637–2167)	693 (534–900)	428 (215–851)	160 (91–282)	1738 (1257–2406)	1071 (803–1430)	6152 (5300–7102)	228 (187–278)	6380 (5508–7380)
Aged <5 years									
Studies	14 (3)	20 (7)	2 (0)	14 (4)	14 (4)	25 (1)	65 (13)	24 (6)	89 (19)
Incidence†	22.6 (15.3–33.4)	19.8 (14.6–27)	12.1 (8.6–17.2)	7.3 (4.6–11.6)	17.8 (12.2–26.1)	17.3 (13.4–22.3)	19.7 (17.1–22.7)	9.9 (7.4–13.3)	..
Number of episodes (thousands)‡	3014 (2040–4454)	1525 (1124–2071)	873 (621–1241)	393 (248–624)	3120 (2193–4692)	2014 (1560–2596)	11373 (9872–13104)	569 (425–764)	11942 (10297–13869)
Very severe ALRI									
Aged <1 year									
Studies	6 (1)	11 (0)	7 (2)	12 (7)	35 (10)	1 (0)	36 (10)
Incidence†	30.8 (21.9–43.2)	8.6 (5.6–13.3)	11.5 (5–26.4)	17.4 (9.7–31.4)	13.7 (10.2–18.5)	8.6 (8.4–8.9)	..
Number of episodes (thousands)‡	868 (617–1217)	130 (84–200)	416 (181–957)	416 (232–751)	1627 (1211–2197)	100 (97–103)	1727 (1309–2300)
Aged <5 years									
Studies	6 (1)	11 (3)	7 (1)	12 (1)	36 (6)	1 (0)	36 (6)
Incidence†	15 (10.4–21.6)	3 (1.9–4.7)	3.7 (1.7–8)	6.3 (3.5–11.2)	5.1 (3.8–6.9)	3 (2.9–3.1)	..
Number of episodes (thousands)‡	1772 (1209–2598)	179 (89–358)	622 (219–1758)	729 (407–1306)	2794 (1980–3983)	173 (167–178)	2967 (2147–4162)

Data in parentheses are imputed number of studies or 95% CI. ALRI=acute lower respiratory infection. *Data include American Indian and Alaska native populations in the USA because the socioeconomic and demographic risk factors for ALRI in these populations are similar to those in the developing countries. †Data are incidence meta-estimates from random effects model. ‡Number of episodes globally in 2010 is the sum of the episodes in children residing in developing and industrialised countries in that year.

Table 1: Estimates of incidence (per 1000 children per year) and the number of episodes of severe ALRI and very severe ALRI in children younger than 5 years admitted to hospital in 2010, by WHO regions

For *The State of the World's Children 2012* see http://www.unicef.org/sowc2012/pdfs/SOWC%202012-Main%20Report_EN_13Mar2012.pdf

For the *2010 World Population Prospects* see http://esa.un.org/unpd/wpp/unpp/panel_population.htm

in 2010 (table 1). We estimate that about 15% (95% CI 10.2–20.8) of all infants and 11% (7–16.3) of children aged 12–59 months admitted with severe ALRI have hypoxaemia. However, the prevalence of hypoxaemia in these children is highly variable across study sites and regions (appendix pp 42–43).

Findings from 28 unpublished studies show that the incidence of admissions for severe ALRI was higher in boys than in girls for all age groups and regions; this sex difference was greatest in studies from South Asia (figure 3). We identified two studies that reported data for residence of children with the Geographic Information System, which showed that disease incidence generally decreased with increasing distance from hospital, except at one site in which admission rates were low for children living within 2 km of hospital (appendix p 46).

We identified four unpublished studies that used both active community-based case ascertainment and had a hospital group for passive case ascertainment (appendix p 33). The proportion of children with chest wall indrawing identified in the community that were treated in hospital varied greatly between these studies (median proportion 0.5, IQR 0.4–0.6). We used this proportion and data for health-care use for ALRI from DHS and MICS databases to estimate that about 19 million episodes of severe ALRI occurred in children aged 0–59 months globally in 2010 (figure 4). This preliminary estimate is consistent with published and well accepted incidence and mortality estimates and is within the confidence intervals of the previous global estimate (figure 4).¹²

We sought to describe the variation in incidence of admissions for severe ALRI in children aged younger than 5 years between 2008 and 2010, mainly during the influenza A H1N1 pandemic in 2009–10. Eight studies (see appendix pp 14–15 for study numbers U7, U9, U11, U17, U18, U22, U25, U26) had data for 2007–08 and 2009–10. Overall, a 32.5% (95% CI 31–33.9; $p < 0.0005$) increase was recorded in the incidence of admissions for severe ALRI between 2007–08 and 2009–10. However, the reported individual rates varied substantially and did not differ in neonates. Similarly, with data from eight studies we noted a 40% (33–47) increase in incidence of admissions for very severe ALRI, again restricted to the post-neonatal population.

We identified ten published^{11,14,21,24,35,40,41,63,64,66} and 27 unpublished studies (appendix pp 34–35) providing data for in-hospital case fatality in children aged younger than 5 years admitted with severe ALRI, and 16 unpublished studies (appendix p 36) reporting case fatality for very severe ALRI. We estimated that the hospital-based case-fatality ratio was 2.3% (95% CI 1.6–3.4; table 2) in children aged 0–59 months admitted with severe, and 6.1% (4.6–8.1) for those with very severe ALRI in developing countries in 2010, with the highest rates reported in studies from Africa; by contrast, estimated case-fatality ratios in industrialised countries were 0.6% (0.4–0.8; table 2) and 3.9% (3.1–4.8), respectively.

We applied the in-hospital meta-estimates of case fatality for the developing and industrialised regions to the incidence meta-estimates for those regions and

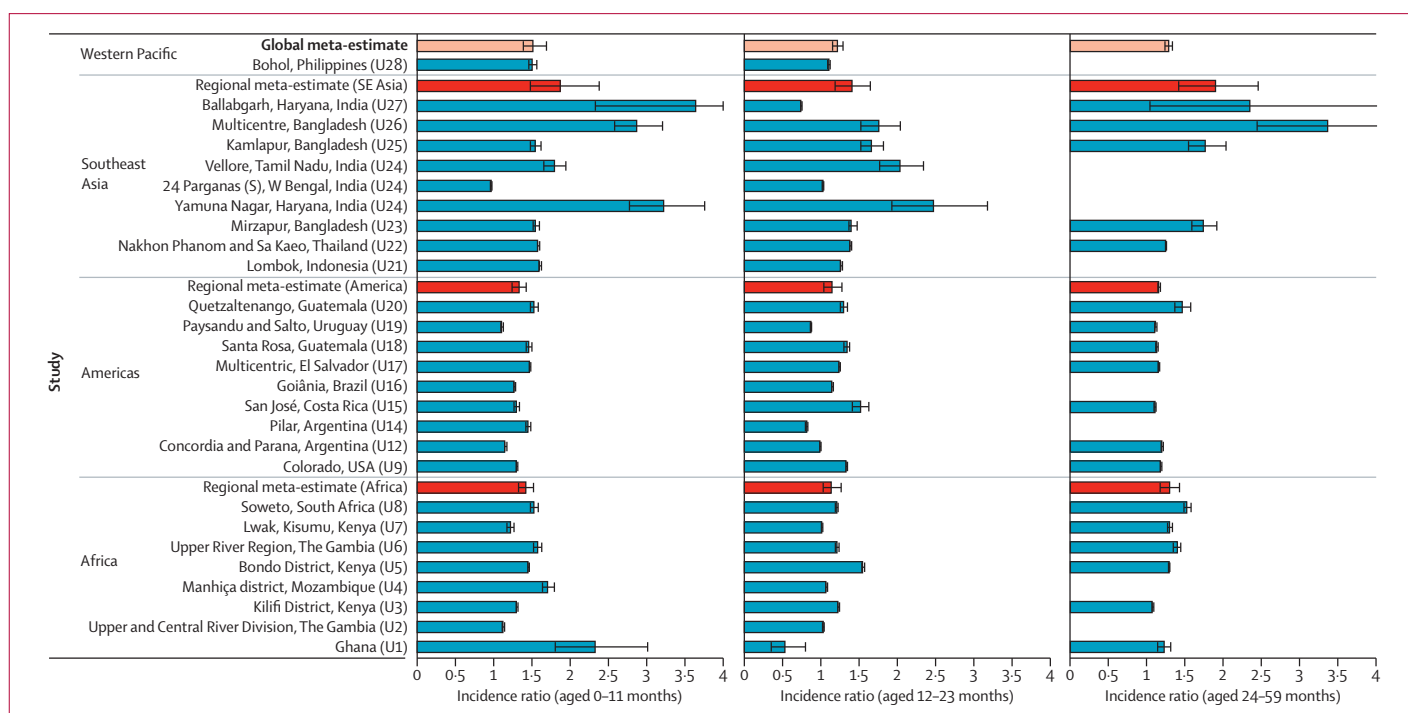


Figure 3: Incidence of admissions for severe acute lower respiratory infection in boys versus girls aged 0–59 months. Error bars show 95% CIs. Appendix pp 14–16 show details of the unpublished studies and study numbers.

estimated that worldwide in 2010, severe ALRI resulted in about 0·3 million in-hospital deaths in children aged 0–4 years, and 67% of these deaths were in young children who presented with signs of very severe ALRI on admission (panel). The case-fatality ratio was 9% (95% CI 1–18) higher in girls ($p=0\cdot01$) aged 0–11 months than in boys of this age, but did not differ significantly ($p=0\cdot49$) by gender in children aged 12–59 months, in whom the ratio was 6% (–13 to 22) higher in boys ($p=0\cdot49$).

Discussion

We estimated that in 2010, there were about 12 million episodes of hospital admissions for severe and 3 million for very severe ALRI. We further estimated that severe or very severe ALRI resulted in about 0·3 million deaths in hospitals in young children. 99% of these deaths were in developing countries, and in-hospital deaths were about 19% (uncertainty range 12–41%, based on extreme combinations of numerator and denominator 95% CI values) of the estimated total number of ALRI deaths in young children in 2010. The incidence of admissions for severe ALRI were more than three times higher in neonates and about 1·3 times higher in infants aged 0–11 months than the overall rate in young children aged 0–59 months. Estimates are very variable within and between countries and regions and across different study periods (table 1, table 2, appendix pp 17–30).

Several factors affect these estimates: method of case ascertainment, precise case definitions for the various categories of admission, geographical location of the study sites, cultural factors, and health-care seeking behaviour of the population. Hence, the true uncertainties around these estimates are larger than those expressed in a standard 95% CI that we report. We have attempted to reduce these biases by using strict case definitions and minimum quality criteria for included studies. Estimates from developing and industrialised countries are not strictly comparable because case definitions in developing countries tend to be based on simple clinical syndromic criteria, with no requirement for results of investigations. Health information systems in developing countries do not typically provide accurate information about the regional and national burden of severe ALRI on hospital services, despite this information being of key importance for the planning of these services. Therefore, such estimates could be useful in the many settings where data are scarce. The incidence meta-estimate for admissions of severe ALRI in developing countries derives largely from studies in which the catchment population had fairly good access to care, and where study interventions might have changed health-care seeking behaviour of participants. We recognise that many children with severe ALRI in developing countries do not receive hospital care. Therefore, our global and regional estimates are likely to underestimate the true burden of severe ALRI, but rather show the burden of

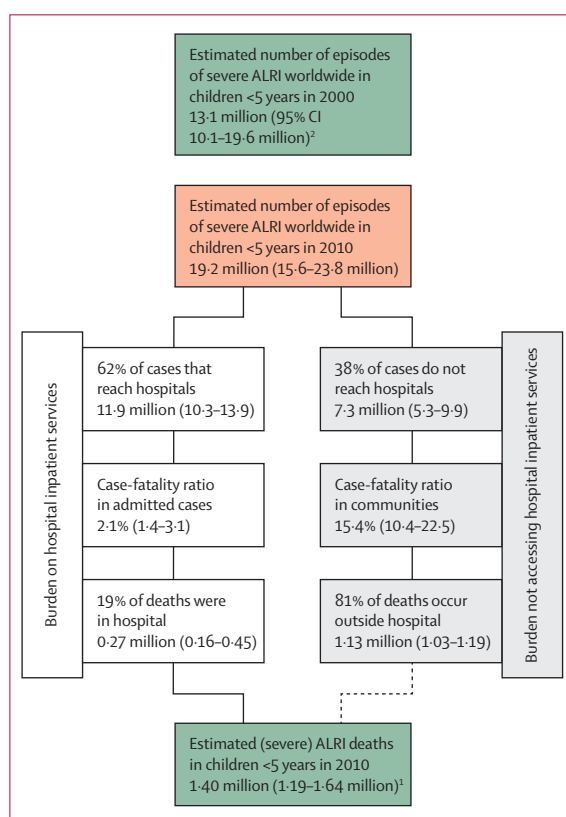


Figure 4: Global burden of severe acute lower respiratory infection, including burden on hospital services

Understanding how these estimates fit with previously reported estimates of the global burden of acute lower respiratory infection (ALRI) is relevant for development of health policies for control of disease mortality. The dark green boxes show previously reported estimates of the global burden of severe ALRI (based on 28 community-based studies of ALRI morbidity) and the burden of ALRI-related deaths (based on independent data that combined vital registration data and data from multicause mortality studies, mainly with verbal autopsy) in young children. Our study (white boxes), based on data from hospital-based studies, introduces a health systems perspective to these previous estimates, which were based mainly on community based studies. We used the estimate for admissions of severe ALRI and available information about health facility use in different global regions to derive an estimate of the possible cases of severe ALRI in the community (orange boxes). The grey boxes show the burden of childhood cases of severe ALRI not accessing hospital inpatient services.

such infection on hospital services, with the assumption that the level of health-care access and use is similar to that in the included 89 studies.

We estimated the extent to which these hospital-based data underestimate the true incidence of severe ALRI in developing countries with poor access to and use of hospital care (figure 4). Although based on indicator data from DHS and MICS for seeking of appropriate health care for children with reported signs of ALRI (rather than care sought for severe ALRI), our estimate of severe ALRI in young children receiving hospital care is broadly consistent with that (49%, IQR 36–62%) from the four hospital studies used in the second of our two analytical approaches.³ Furthermore, our estimates are consistent with those reported elsewhere (figure 4).^{1,2}

	Aged 0–11 months		Aged 12–59 months		Aged 60–59 months	
	Studies	CFR (%)	Studies	CFR (%)	Studies	CFR (%)
Africa	9	3.8% (2.4–5.9)	8	1.9% (1.2–3.2)	11	3.9% (2.7–5.5)
Americas	10	1.6% (1.1–2.4)	10	0.6% (0.2–1.3)	11	1.3% (0.8–1.9)
Eastern Mediterranean	1	9.9% (8.6–11.5)	2	7.6% (4.1–13.9)
Europe	1	0.4% (0.3–0.5)
Southeast Asia	6	2.6% (1.4–4.7)	4	0.3% (0.1–0.9)	9	2.1% (1.1–4)
Western Pacific	1	2.4% (1.3–4.3)	3	2.3% (1.7–3.2)
Developing	26	2.4% (1.7–3.6)	21	0.8% (0.4–1.3)	34	2.3% (1.6–3.4)
Industrialised	1	0.8% (0.7–0.9)	1	0.3% (0.2–0.5)	3	0.6% (0.4–0.8)
Global	27	2.3% (1.5–3.4)	22	0.7% (0.4–1.2)	37	2.1% (1.4–3.1)

Data in parentheses are 95% CI. CFR=case-fatality ratio.

Table 2: Case-fatality ratio due to severe acute lower respiratory infections in children younger than 5 years who were admitted, by region

Panel: Estimated new cases per year, case-fatality ratio, and mortality in children younger than 5 years admitted to hospital for severe acute lower respiratory infections (ALRI)

Children admitted for severe ALRI

- a Estimated new cases per year in developing countries: 11 372 600 (95% CI 9 871 650–13 104 470)
- b Estimated case-fatality ratio in developing countries: 2.3% (1.6–3.4)
- c Estimated mortality in hospitals in developing countries: $a \times b = 261\,570$ (157 950–445 550)
- d Estimated new cases per year in industrialised countries: 569 020 (425 330–764 440)
- e Estimated case-fatality ratio in industrialised countries: 0.6% (0.4–0.8)
- f Estimated mortality in hospitals in industrialised countries: $d \times e = 3410$ (1700–6120)
- g Estimated global mortality: $c + f = 264\,980$ (159 650–451 670)

Children admitted for very severe ALRI

- h Estimated new cases per year in developing countries: 2 794 080 (1 980 100–3 983 300)
- i Estimated case-fatality ratio in developing countries: 6.1% (4.6–8.1)
- j Estimated mortality in hospitals in developing countries: $h \times i = 170\,440$ (91 090–322 650)
- k Estimated new cases per year in industrialised countries: 172 430 (166 680–178 180)
- l Estimated case-fatality ratio in industrialised countries: 3.9% (3.1–4.8)
- m Estimated mortality in hospitals in industrialised countries: $k \times l = 6730$ (5170–8550)
- n Estimated global mortality: $j + m = 177\,170$ (96 260–331 200)

The high number of severe ALRI episodes mostly shows inadequate care-seeking behaviour or poor access to hospital care, or both, in some settings. For example, many children referred for hospital care do not attend because of cost or cultural factors.⁶⁷ This estimate also shows the extent of the large referral burden on hospital services in developing countries, which suggests a need for substantially increased investment in hospital capacity for inpatient and outpatient services, both in terms of human resources and for provision of relevant drugs and supplies for paediatric care. New approaches to increasing of treatment coverage for severe pneumonia, as defined by WHO, in communities that are underserved by

hospitals have been effective in Asian settings.^{68,69} WHO recommendations, based on findings from these controlled trials in Asia⁷⁰ for management of cases of WHO severe pneumonia with oral antibiotics at home is one strategy that could be effective in some settings.

The analysis in figure 4 shows a general consistency in estimates and has important policy implications: although 62% of children manage to reach hospitals, most deaths still take place outside hospitals. This result is attributable to the large difference in case fatality between hospital-treated and non-hospital-treated severe ALRI. Furthermore, the findings suggest that even if very high rates of access and care seeking were achieved, the number of deaths might still be high. In addition to strategies to increase coverage of pneumococcal vaccination in young children, scaling up of community case management of childhood ALRI (including management of WHO severe pneumonia when appropriate) should be regarded as an effective strategy that could help to reduce the remaining burden of mortality, remove the burden on hospital services, and improve equity in reduction of child mortality.

Findings from two studies (appendix p 46) showing that incidence of admissions for severe ALRI decreased with increasing distance from the hospital were consistent with previous reports^{71,72} and emphasise that access to hospital care is an important determinant of deaths from pneumonia in children in developing countries. We noted a consistently higher incidence of admissions for severe ALRI in boys than in girls. Although this increased risk could be attributable to the smaller airway size in young boys than in young girls,⁷³ the substantially heightened sex differences in South Asian studies (India, Pakistan, and Bangladesh) probably shows the importance of cultural factors, such as preference in seeking medical care for boys.^{74,75} Global burden of disease estimates tend not to include estimates by sex for child mortality from pneumonia; therefore, to what extent sex differences affect pneumonia mortality is uncertain. These differences, especially those in South Asia, merit further study and programmatic attention because they could represent substantial health inequity. Investigators of future epidemiological studies should make increased efforts to gather, analyse, and report gender-specific data to increase the attention given to this important issue.

Hypoxaemia is a key predictor of ALRI mortality⁷⁶ and an important indicator of severity. Hypoxaemia prevalence estimates were variable across study sites and defined by factors such as altitude of the study site. 12.6% of severe cases had hypoxaemia, which is consistent with findings from a systematic review and meta-analysis.⁷⁶ Our estimates suggest that every year about 1.5 million children admitted with severe ALRI need oxygen treatment. The estimates further emphasise and quantify the need for pulse oximetry equipment and related staff training for identification of children with

hypoxaemia, because clinical signs are poor indicators of this complication.⁷⁶

We estimate that about a third of all admissions for severe ALRI meet clinical criteria for very severe ALRI and need second-line parenteral treatment with antibiotics; however, substantial heterogeneity exists. In general, the incidence estimates for African countries are about five times higher than those for other developing regions. This finding could show poor access to care in these regions, leading to delays in antibiotics and frequent progression to more severe disease. Furthermore, the estimates are consistent with severe falciparum malaria in endemic areas being misclassified as severe ALRI in settings with few diagnostic facilities.⁷⁷

In 2010, during the influenza A H1N1 pandemic, our estimates showed an increase in the incidence of admissions for severe and very severe ALRI compared with estimates from the same sites for 2008. This finding could result from increased community awareness about respiratory illness during the pandemic period, leading to increased care seeking and hospital admission or because of an annual variation in the incidence of severe ALRI. However, the increase in admission could be partly explained by disease due to the pandemic predisposing to subsequent bacterial pneumonias.⁷⁸ This relation needs to be investigated because the ability of health services to respond to a substantial increase in childhood severe ALRI could be an important component of pandemic influenza preparedness and for reducing of influenza-related childhood mortality.

No data are available for several regions worldwide with large high-burden populations⁷⁹—eg, WHO's Eastern Mediterranean region and much of sub-Saharan Africa. Our estimates of the incidence of admissions for severe ALRI could be used to assess the needs for equipment, such as pulse oximeters and oxygen concentrators, and for drugs in hospitals in developing countries where health information systems cannot supply these data. The fairly low estimated percentage of overall deaths that take place in hospital emphasises that access to hospital care is inadequate in many developing countries. Investment should be made to improve such access and to introduce new strategies, such as community case management for cases presently classified as WHO severe pneumonia. Access to care, sex inequities in care seeking, and appropriate case management of children with severe and very severe pneumonia needs urgent assessment if further reductions in childhood deaths from pneumonia are to be achieved.

Contributors

HN, HC, and MWW conceptualised the study. HN led the literature search, data collection, data analysis, data interpretation, and writing of the report. JSFZ did the literature search and data extraction from Chinese language databases. EAFS, EA-B, DRF, GAM, BDG, JCM, ZAB, AR, HCB, SMAZ, RJS, MGL, AC, AG, CC, AK, AA, AWC, ALA, MO, ROR, MH, JPM, SAM, SAM, NB, SEA, WAB, and RFB contributed to collection and analysis of primary data, data interpretation, and critically reviewed the manuscript. PH did the literature search and data extraction from English language databases. SAQ, JAGS, and MWW

contributed to data interpretation and critically reviewed the manuscript. IR and HC participated in data interpretation, contributed to report writing, and critically reviewed the manuscript. All other members of the Severe ALRI Working Group contributed to data collection, data analysis, and critically reviewed the manuscript. All authors read and approved the final draft of the manuscript.

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Conflicts of interest

AA has received research grants, honoraria for participation in advisory boards, and travel grants from GlaxoSmithKline (GSK), Wyeth, and Pfizer. BDG works for Agence de Médecine Préventive, which receives unrestricted funding from Sanofi Pasteur, and has received grant support from Crucell, GSK, Merck, Pfizer, and Sanofi Pasteur. JAGS has received research funding from GSK and a travel grant from Merck. SAM has been a clinical trialist in studies of vaccines against pneumonia-causing pathogens from GSK, Pfizer, Sanofi-Aventis, Novartis, and MedImmune; his institution has received research grants from GSK, Pfizer, and

Novartis; and he has been on the speaker's bureau of GSK, Pfizer, and Sanofi-Aventis, has received travel support and honoraria, and has acted on advisory boards of GSK, Pfizer, and Novartis. HNo is part of ARIVAC consortium that includes Sanofi Pasteur, undertook a phase 3 trial of an 11-valent pneumococcal conjugate vaccine (Sanofi Pasteur, Lyon, France) in the Philippines in 2002–04, and has received research funding from GSK. ALA has received research grant from GSK, financial support from Pfizer and GSK to attend meetings, and has served as an adviser to Pfizer. WAB has received funding from the Bill & Melinda Gates Foundation for vaccine-related work related to childhood pneumonia; donation of vaccine from Sanofi Pasteur for a vaccine trial against early childhood pneumonia; project funding from Sanofi Pasteur for pneumococcal vaccine trials and a study in pneumococcal pneumonia disease burden in young children; and has been on the speakers bureau for Sanofi Pasteur. SSM is an employee of the Bill & Melinda Gates Foundation. SAQ, AWM, and MWW are WHO staff members. All other authors declare that they have no conflicts of interest.

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